**MeshMonk: open-source large-scale intensive 3D facial phenotyping**

**Keywords:** automatic landmarking; automated phenotyping; non-rigid registration; phenomics; morphometrics; 3D; face

In the post-genomics era, an emphasis has been placed on disentangling ‘genotype-phenotype’ connections so that the biological basis of complex phenotypes can be understood. While advances have been made to characterize genomic data on a high-throughput level, our ability to efficiently and comprehensively characterize phenotypic data is lagging. Anthropometric studies of morphology have traditionally relied on a sparse set of landmarks manually placed on images, based on which linear distances and angles are calculated, to be used in downstream genetic association studies. This requires the tedious manual placement of landmarks on many images, a process which is error prone and sensitive to differences among observers. Here, we report a toolbox for fast and reproducible high-throughput phenotyping of 3D images. While we demonstrate the utility of this method using 3D facial images, the procedure can also be applied to 3D scans of other complex morphological structures such as the human brain and skeletal bones.

Given a facial image (target) with five crude positioning landmarks, a rigid registration is first used to orient an anthropometric mask (reference) to the target scan. Then, using a weighted k-nearest neighbors and a visco-elastic transformation model, the reference is transformed to fit the specific shape of the target. For facial scans, this results in homologous spatially dense (N=7,160) quasi-landmark configurations for all 3D images. As validation, a dataset (N=40) with 19 manually-placed landmarks was superimposed onto the reference to identify the closest barycentric coordinate on the mask. These coordinates were then projected back onto the training faces in a leave-one-out method and the manual and automatic landmark placements compared.

We demonstrate that this method is highly accurate, with an average Euclidean distance between the manual and automatic placements of ~1.2 mm. The process is robust to variation due to scan quality, camera systems, and genetic ancestry. Though validated using 19 landmarks for comparison with traditional methods, this method allows for automated dense phenotyping, freeing the researcher from the use of a limited number of landmarks and allowing them to comprehensively explore variations in surface shape. This expansion opens up an exciting avenue of study in assessing genomic and phenomic data to better understand the genetic contributions to complex morphological traits.